

Official title: Changes in cerebral oxygenation based on intraoperative ventilation strategy

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## **Abstract**

**Introduction:** Cerebral oxygenation can be monitored clinically by cerebral oximetry (rSO<sub>2</sub>) using near infrared spectroscopy (NIRS). Changes in rSO<sub>2</sub> have been shown to precede changes in pulse oximetry, providing earlier detection of clinical deterioration. Cerebral oximetry values may be affected by various factors, including changes in ventilation. The current study evaluates changes in rSO<sub>2</sub> during intraoperative changes in mechanical ventilation.

**Methods:** Following IRB approval, tissue and cerebral oxygenation were monitored intraoperatively using NIRS. Prior to anesthetic induction, the NIRS monitor was placed on the forehead and over the deltoid muscle to obtain baseline values. NIRS measurements were recorded each minute over a 5-minute period during general anesthesia at four phases of ventilation: 1) normocarbida (35-40 mmHg) with a low fraction of inspired oxygen (FiO<sub>2</sub>) of 0.3; 2) hypocarbida (25-30 mmHg) and low FiO<sub>2</sub> of 0.3; 3) hypocarbida and a high FiO<sub>2</sub> of 0.6; and 4) normocarbida and a high FiO<sub>2</sub>. NIRS measurements during each phase were compared to sequential phases using paired t-tests.

**Results:** The study cohort included 30 adolescents. Baseline cerebral and tissue oxygenation were  $81 \pm 9$  and  $87 \pm 5$ , respectively. During phase 1, cerebral rSO<sub>2</sub> was  $83 \pm 8$  and decreased to  $79 \pm 8$  in phase 2 (hypocarbida and low FiO<sub>2</sub>). Cerebral oxygenation partially recovered during phase 3 ( $81 \pm 9$ ) with the increase in FiO<sub>2</sub> and then returned to baseline during phase 4 ( $83 \pm 8$ ). Each sequential change (e.g., phase 1 to phase 2) in cerebral oxygenation was statistically significant ( $p < 0.01$ ). Tissue oxygenation was unchanged during the study phases and remained at 87-88 throughout.

**Discussion:** Cerebral oxygenation declined during general anesthesia with the transition from normocarbida to hypocarbida conditions. The rSO<sub>2</sub> decrease related to hypocarbida was easily reversed with a return to baseline values by the administration of supplemental oxygen (60% versus 30%).

## **Introduction**

A key component of intraoperative care is the assurance of adequate cardiac output and delivery of oxygen to the tissues. While routine intraoperative care includes monitoring of blood pressure and systemic oxygenation (pulse oximetry), there is clinical interest in measuring end-organ tissue oxygenation. As such, monitors of tissue oxygenation such as cerebral oximetry using near infrared spectroscopy (NIRS) are being used more commonly in anesthesia practice. The NIRS monitor consists of a non-invasive adhesive sensor with a laser light source and two photodetectors. Using optical technology based on the relative absorption of infrared light by different hemoglobin species, the monitor generates a measurement of regional tissue oxygen saturation (rSO<sub>2</sub>).<sup>1</sup> Most commonly applied to the forehead, the device measures cerebral oxygenation, but can be used to detect regional tissue saturation elsewhere in the body. Data in both adult and pediatric literature suggest that monitoring and maintaining cerebral oxygenation may improve perioperative neurological outcomes.<sup>2,3</sup> Most established and applied during cardiac surgery, the NIRS monitor is being used increasingly in the operating room and intensive care unit (ICU) to monitor cerebral perfusion and guide management in various clinical scenarios. A decrease in cerebral oxygenation correlates with events of clinical deterioration such as arrhythmia, hypotension, and hypoxia.<sup>4</sup> Changes in cerebral oxygenation have been shown to precede those in pulse oximetry, providing an earlier detection of clinical deterioration.<sup>5</sup>

In the adult population, alterations in inspired oxygen concentration and expired carbon dioxide have been shown to influence cerebral oxygenation.<sup>6</sup> Various patient, surgical, and anesthetic factors may influence intraoperative ventilation choices (minute ventilation and the fraction of inspired oxygen) and the resultant arterial partial pressure of oxygen (PaO<sub>2</sub>) and carbon dioxide (PaCO<sub>2</sub>).<sup>7-11</sup> Examples include laparoscopic surgery, intrathoracic surgery, airway surgery, patient positioning, and co-morbid conditions.<sup>8,9</sup> Furthermore, various factors

including a decrease in the metabolic rate related to general anesthesia may result in inadvertent hyperventilation during routine intraoperative care.<sup>9</sup> Understanding how ventilation affects cerebral oxygenation is of clinical importance, especially when faced with other physiologic changes such as anemia and decreased cardiac output that may impact tissue and cerebral oxygen delivery. The relationship between ventilation and cerebral rSO<sub>2</sub> has not been examined in the pediatric population. The current study seeks to evaluate changes in cerebral and tissue rSO<sub>2</sub> during intraoperative changes in mechanical ventilation parameters.

## **Methods**

Institutional Review Board approval and verbal consent from a parent and assent from the patient were obtained. This study was registered with ClinicalTrials.gov (NCT02651103). Enrolled patients were children undergoing a major surgical procedure requiring placement of an arterial cannula. Prior to anesthetic induction, the NIRS monitor was placed on the forehead and over the deltoid muscle, in addition to standard American Society of Anesthesiologists (ASA) monitors. Baseline values for cerebral and tissue oxygenation were obtained using NIRS. After the induction of general anesthesia and placement of an endotracheal tube, an arterial cannula was placed and NIRS values were again measured at the following four phases of ventilation with variation of the inspired oxygen concentration (FiO<sub>2</sub>) and end-tidal carbon dioxide value (ETCO<sub>2</sub>):

- 1) normocarbida (ETCO<sub>2</sub> 35-40 mmHg) and low FiO<sub>2</sub> (0.3);
- 2) hypocarbida (ETCO<sub>2</sub> = 25-30 mmHg ) and low FiO<sub>2</sub> (0.3);
- 3) hypocarbida (EICO<sub>2</sub> = 25-30 mmHg) and high FiO<sub>2</sub> (0.6); and
- 4) normocarbida (ETCO<sub>2</sub> = 35-40 mmHg) and high FiO<sub>2</sub> (0.6).

To ensure the accuracy of the ETCO<sub>2</sub> value, arterial blood gas was obtained prior to the start of the study and the ETCO<sub>2</sub> was validated using the PaCO<sub>2</sub> measurement. At baseline and during each phase of ventilation, NIRS measurements were recorded every minute over a 5-minute period. Heart rate (HR) and blood pressure (BP) were recorded at each of the sampling intervals and hemodynamic variables maintained constant by adjustments in the continuous infusion of remifentanyl. Depth of anesthesia was maintained at a constant value with the administration of inhaled desflurane which was titrated to maintain the bispectral index (BIS) at 50-60.

The average of available NIRS measurements within each ventilation phase was obtained and used to compare sequential phases with paired t-tests. A planned sample size of 30 patients was selected to be comparable to previous studies in the adult population, and to be consistent with study feasibility and projected patient enrollment. Due to the exploratory nature of this investigation in a pediatric population, no *a priori* power analysis was performed. Data analysis was performed in Stata/IC 13.1 (College Station, TX: StataCorp LP), and two-tailed  $p < 0.05$  was considered statistically significant.

## **Results**

The study cohort included 30 patients (13 males and 17 females, age  $15 \pm 3$  years, and weight  $55 \pm 15$  kg). Cohort characteristics are summarized in **Table 1**. Changes in heart rate and blood pressure over the course of the study are summarized in **Table 2**. The peripheral oxygen saturation by pulse oximetry remained at 99-100% throughout the study. The baseline cerebral and tissue rSO<sub>2</sub>, prior to anesthetic induction while breathing room air, were  $81 \pm 9$  and  $87 \pm 5$ , respectively. During phase 1, cerebral rSO<sub>2</sub> was  $83 \pm 8$  and decreased to  $79 \pm 8$  in phase 2 (hypocarbica and low FiO<sub>2</sub>). Cerebral oxygenation recovered, returning to baseline values, during phase 3 ( $81 \pm 9$ ) and phase 4 ( $83 \pm 8$ ). Each sequential change (e.g., phase 1 to

phase 2) in cerebral oxygenation was statistically significant ( $p < 0.01$ ; **Table 3**). Tissue oxygenation increased from  $87 \pm 8$  in phase 1 to  $88 \pm 7$  in phase 2 ( $p = 0.002$ ); remained at  $88 \pm 7$  in phase 3; and decreased to  $87 \pm 8$  in phase 4 ( $p = 0.023$ ; **Table 3**).

## **Discussion**

Cerebral oxygenation as measured by NIRS may provide valuable information regarding cerebral oxygen delivery and utilization in critically ill patients both in the operating room and the ICU settings. Intraoperatively, it may help guide anesthetic care, as studies in adults have shown that maintaining adequate values on NIRS may improve neurological outcomes.<sup>2,12</sup> One of the primary regulators of cerebral blood flow is  $\text{PaCO}_2$ . Hypocarbica results in a direct effect on the cerebral vasculature with vasoconstriction and a decrease in cerebral blood flow (CBF). For every 1 mmHg change in  $\text{PaCO}_2$ , CBF changes by 1-2 mL/100 gm/minute. As there is no impact on the cerebral metabolic rate for oxygen related to changes in  $\text{PaCO}_2$ , the decrease in CBF may lead to a decrease in cerebral oxygenation. In our study, cerebral oxygenation as measured by NIRS declined during general anesthesia with the transition from normocarbica to hypocarbica conditions. Despite this decrease, no clinical impact would be expected as the starting  $\text{rSO}_2$  was high, the change with hyperventilation was small, and the resultant value remained well above the reported threshold for concern.

Our data demonstrate that even in clinically stable patients,  $\text{PaCO}_2$  remains an important determinant of CBF and cerebral oxygenation. Changes in CBF related to alterations in intraoperative ventilation may have a greater impact in critically ill patients when other factors which impact  $\text{rSO}_2$ , such as hemoglobin values and cardiac output, may be affected. We have previously noted the potential impact of the combination of anemia, hypotension and hypocarbica on  $\text{rSO}_2$ , suggesting that close attention to control of ventilation is important during intraoperative care where inadvertent hyperventilation is commonplace.<sup>7,13</sup>

Additionally, these data demonstrate that the rSO<sub>2</sub> decrease related to hypocarbia was reversed by the administration of supplemental oxygen (60% versus 30%). In clinical scenarios where hyperventilation is required, such as to reduce intracranial pressure when there is impending cerebral herniation or to blunt the respiratory drive, increasing the FiO<sub>2</sub> may be pertinent to offset any reduction in cerebral oxygenation related to decreases in CBF. Thiagarajan et al. evaluated 18 adults with traumatic brain injury to determine the changes in cerebral jugular venous oxygen saturation (SjvO<sub>2</sub>) and arteriovenous oxygen content difference (AVDO<sub>2</sub>) in response to changes in PaO<sub>2</sub> and PaCO<sub>2</sub>.<sup>14</sup> SjvO<sub>2</sub> decreased from 66% ± 3% to 56% ± 3% when PaCO<sub>2</sub> decreased from 30 to 25 mmHg at a PaO<sub>2</sub> of 100-150 mmHg. The SjvO<sub>2</sub> values were significantly greater when the PaO<sub>2</sub> was 200-250 mmHg (77% ± 4% and 64% ± 3%) at PaCO<sub>2</sub> values of both 30 and 25 mmHg. The authors concluded, as we did in our study, that decreases in cerebral oxygenation (manifested as decreases in SjvO<sub>2</sub>) associated with a decrease in PaCO<sub>2</sub>, were offset by increasing the PaO<sub>2</sub>. These data are particularly relevant given the literature demonstrating episodes of cerebral ischemia and worse neurologic outcome in patients with traumatic brain injury who are exposed to hypocarbia.<sup>15</sup>

Similar results have been noted in the adult population by other investigators using various monitors of cerebral oxygenation. All of these studies have demonstrated that both alterations in inspired oxygen concentration and expired carbon dioxide impact cerebral tissue oxygenation. Tisdall et al. measured the cerebral tissue oxygenation index (TOI) in 15 adults under hypoxic, hyperoxic, hypo- and hyper-carbic conditions.<sup>6</sup> Hypoxemic and hypocarbic conditions resulted in a decrease of the TOI by 7.1% and 2.1% respectively while hyperoxia and hypercarbia led to increases of 2.3% and 2.6%. Picton et al. reported a 7% decrease of rSO<sub>2</sub> after beach-chair positioning in adults maintained at an FiO<sub>2</sub> of 0.3 and ETCO<sub>2</sub> of 30 mmHg which was reversible by decreasing ventilation and increasing the FiO<sub>2</sub>.<sup>10</sup> The same investigators reported that the rSO<sub>2</sub> was an average of 8% higher with an FiO<sub>2</sub> of 1.0 versus

0.3 at an ETCO<sub>2</sub> of 30-35 mmHg. Bouzat et al reported a 5% reduction in rSO<sub>2</sub> with hyperventilation in adult patients recovering from cardiac arrest.<sup>16</sup>

Our literature search revealed no previous studies in the pediatric age range that examined the effect of ventilation on cerebral oxygenation. When compared to some of the adult studies, it is not surprising that the decrease in cerebral oxygenation that we noted was smaller than that seen in the adult population, as our patients lacked co-morbid conditions, such as atherosclerotic disease, which might affect CBF. When evaluating intraoperative studies, including the present work, one must also consider the impact that the anesthetic agents may have on the findings as specific anesthetic agents may affect cerebral metabolic rate for oxygenation and thereby mitigate the effects of the decrease in CBF on cerebral oxygenation.<sup>17</sup> As the current study focused on adolescents, extrapolation of these data to younger populations is likely infeasible, and additional trials are needed in these age groups to determine the impact of changes in ventilation on cerebral rSO<sub>2</sub>.

As expected, no major changes in tissue oxygenation were noted related to hyperventilation, and the changes in cerebral rSO<sub>2</sub> under the specific study conditions had no clinical impact. The change from baseline was minimal, and the low value even under hypobaric conditions was well above the NIRS monitor's low threshold value for concern. However, the impact of hypocarbia must be considered when co-morbid conditions or ongoing acute issues, such as anemia or hypotension, may further impact cerebral oxygenation. In specific clinical scenarios where hyperventilation is clinically indicated, the impact on cerebral oxygenation can be mitigated by increasing the FiO<sub>2</sub>.



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**Table 1. Study cohort characteristics**

<b>Variable</b>	<b>N (%) or Mean (SD)</b>
<b>Gender</b>	
<b>Male</b>	13 (43%)
<b>Female</b>	17 (57%)
<b>Age (years)</b>	15 (3)
<b>Weight (kg)</b>	55 (15)
<b>ASA status</b>	
<b>1</b>	5 (17%)
<b>2</b>	16 (53%)
<b>3</b>	8 (27%)
<b>4</b>	1 (3%)

**Table 2. Hemodynamic parameters during the four study phases**

<b>Variable</b>	<b>Baseline</b>	<b>Phase 1</b>	<b>Phase 2</b>	<b>Phase 3</b>	<b>Phase 4</b>
Heart rate (beats/minute)	90 (16)	82 (14)	83 (14)	82 (13)	78 (11)
sBP (mmHg)	100 (22)	87 (14)	86 (11)	90 (11)	87 (12)
dBp (mmHg)	62 (15)	53 (9)	53 (9)	55 (7)	51 (7)
MAP (mmHg)	73 (16)	64 (10)	64 (9)	66 (8)	64 (8)

HR = heart rate; sBP = systolic blood pressure; dBp = diastolic blood pressure; MAP = mean arterial pressure

**Table 3. Cerebral and tissue oxygenation during study phases**

rSO2	Study phase					P-value		
	Baseline	Phase 1	Phase 2	Phase 3	Phase 4	2 vs. 1	3 vs. 2	4 vs.3
Tissue	87 (5)	87 (8)	88 (7)	88 (7)	87 (8)	0.002	0.776	0.023
Cerebral	81 (9)	83 (8)	79 (8)	81 (9)	83 (8)	<0.001	0.007	0.009